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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/889,355	07/08/1997	HEIDRUN ENGLER	16930-000811	3379

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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	24

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/889,355	Applicant(s) ENGLER ET AL.	
	Examiner Michael Wilson	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,22,35,36 and 40-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,22,35,36 and 40-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Applicant's arguments filed 5-16-01, paper number 20, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-20, 23-34, 37-39 and 56-61 have been canceled. Claims 21, 22, 35, 36 and 40-55 are pending and under consideration in the instant application. The effective filing date of the claimed invention remains July 8, 1997.

Claim Objections

Claim 22 is objected to because of the following informalities: mucoadhesive is misspelled on line 1 of the clean copy of claim 22. Appropriate correction is required.

Specification

The abstract contains legal language. In addition, the structure in the abstract may be improper. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the

printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Rejections - 35 USC § 112

1. Claims 21, 22, 35, 36 and 40-55 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The specification teaches isolating Impurities I, II and III from BigCHAP; however, the specification does not describe their structure. Since the time of filing, the structure of Impurities I, II and III have been determined (see attached description provided in 09/112,074).

BigCHAP does not correlate to the claims because it does not have the same tertiary nitrogen as Formula I or II.

Impurity I does not have a tertiary nitrogen; therefore, it does not correlate to the claims.

In Impurity II, if X1 is the group on the left of the structure (see attached), Impurity II has the same tertiary nitrogen as BigCHAP; therefore, it does not correlate to the claims. In addition, the specification does not describe X1 as being a cholic acid group (and not deoxycholic acid group). In Impurity II, if X1 is the group on the upper right of the structure of Impurity II, the

specification does not describe the group as having a cholic acid group (and not deoxycholic acid group), or describe the carbon chain between the carboxyl group and the tertiary nitrogen. Nor does the specification describe X2 as being a pentose monosaccharide group. Therefore, the structure of Impurity II is not readily apparent from the specification as originally filed because the specific combination of elements in X1, X2 or X3 could not have been guessed.

In Impurity III, the specification does not describe the impurity as having two cholic acid groups (and not deoxycholic acid groups) as X1 and X2 or X3. The specification does not describe X2 or X3 as a pentose monosaccharide. Therefore, the structure of Impurity III is not readily apparent from the specification as originally filed because the specific combination of elements in X1, X2 or X3 could not have been guessed.

Furthermore, Impurities II and III have a cholic acid having a deletion of the terminal CO_2H which is not disclosed in the specification as originally filed. Cholic acid having a deletion of the terminal CO_2H is not a "cholic acid group" as claimed because it is no longer cholic acid.

Additionally, the specification does not teach any compounds having a deoxycholic acid group, a hexose monosaccharide group, a pentose-pentose disaccharide group, a hexose-hexose disaccharide group, a pentose-hexose disaccharide group, or a hexose-pentose disaccharide group.

Finally, even if the structure of Impurity II and III were readily apparent in the specification as originally filed, the structure of Impurity II and III is not adequate written for all compounds having Formula I or II as claimed which encompasses numerous combinations of X1,

X2 and X3. These structures are significantly different and may have different functions than Impurity II or III. Therefore, Impurities II and III are not adequate to describe the genus claimed.

In conclusion, the specification does not provide adequate written description for a compound having the structure of Formula I or II as claimed.

Applicants argue cholic and deoxycholic acid have 3 carbons. Applicants argument is not persuasive. The structure of cholic and deoxycholic acid as determined in the registry of chemical compounds shows they have an additional COH2 (see attached).

Applicants argue the synthetic scheme for producing Impurity II is disclosed in example 12. Applicants argument is not persuasive because Impurity II (see attached) does not have the structure on pages 6 and 7 of applicants response. It has a different tertiary nitrogen that is different than BigCHAP and a longer carbon chain attached to one of the cholic acid groups (see attached, especially the upper right carbon chain attached to "CA").

2. Claims 21, 22, 35, 36 and 40-55 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

The specification teaches isolating Impurities I, II and III from BigCHAP; however, the specification does not teach their structure. Since the time of filing, the structure of Impurities I, II and III have been determined (see attached description provided in 09/112,074).

BigCHAP does not correlate to the claims because it does not have the same tertiary

nitrogen as Formula I or II.

Impurity I does not have a tertiary nitrogen; therefore, it does not correlate to the claims.

In Impurity II, if X1 is the group on the left of the structure (see attached), Impurity II has the same tertiary nitrogen as BigCHAP; therefore, it does not correlate to the claims. In addition, the specification does not teach X1 is a cholic acid group (and not deoxycholic acid group). In Impurity II, if X1 is the group on the upper right of the structure of Impurity II, the specification does not teach the group as having a cholic acid group (and not deoxycholic acid group), or teach the carbon chain between the carboxyl group and the tertiary nitrogen. Nor does the specification teach X2 is a pentose monosaccharide group. Therefore, the structure of Impurity II is not readily apparent from the specification as originally filed because the specific combination of elements in X1, X2 or X3 could not have been guessed.

In Impurity III, the specification does not teach the compound has two "cholic acid groups" (and not deoxycholic acid groups) as X1 and X2 or X3. The specification does not teach X2 or X3 is a pentose monosaccharide. Therefore, the structure of Impurity III is not readily apparent from the specification as originally filed because the specific combination of elements in X1, X2 or X3 could not have been guessed.

Furthermore, Impurities II and III have a cholic acid having a deletion of the terminal CO_2H which is not disclosed in the specification as originally filed. Cholic acid having a deletion of the terminal CO_2H is not a "cholic acid group" as claimed because it is no longer cholic acid. Therefore, the structure of Impurities II and III is not readily apparent from the specification as

originally filed because it could not have been guessed that the cholic or deoxycholic acid group was attached such that the terminal CO_2H was deleted.

Additionally, the specification does not teach any compounds having a deoxycholic acid group, a hexose monosaccharide group, a pentose-pentose disaccharide group, a hexose-hexose disaccharide group, a pentose-hexose disaccharide group, or a hexose-pentose disaccharide group.

Finally, even if the structure of Impurity II and III were readily apparent in the specification as originally filed, the structure of Impurity II and III does not enable any and all compounds having Formula I or II as claimed which encompasses numerous combinations of X1, X2 and X3. These structures are significantly different and may have different functions than Impurity II or III. Therefore, Impurities II and III are not adequate to enable the genus claimed.

In conclusion, the specification does not enable a compound having the structure of Formula I or II as claimed.

The claims remain rejection for reasons of record because they encompass modifications of the Impurities which are not adequately taught. Applicants argue the three impurities describe in the specification satisfy the requirement that there be a representative number of species. Applicants argument is not persuasive. Impurity I does not have a tertiary nitrogen, and Impurity II has the same tertiary nitrogen as BigCHAP (see attached). Therefore, Impurities I and II are not encompassed by the claims which require a tertiary nitrogen that is different than BigCHAP. The specification does not teach the structure of Impurity III and the specification does not teach

how to modify Impurity III. Without the structure of Impurity III, it would require one of skill in the art undue experimentation to determine how to modify Impurity III.

The specification does not enable treating bladder cancer using the composition claimed in combination with a therapeutic gene (claims 35, 36 and 40) for reasons of record. The state of the art at the time of filing was such that it was unpredictable what combination of vector, promoter, route of administration, dosage, protein of interest, level of expression, and target tissue were required to obtain a desired therapeutic effect (Eck, Verma, Ross and Marshall all of record). The specification discloses administering adenoviral vector encoding RB operatively linked to a promoter combined with BC BigCHAP to mice and obtaining RB expression (example 6; Fig. 9). The specification does not teach administering $1x10^8$ to $5x10^{11}$ particles/ml of an adenovirus encoding RB provides a therapeutic effect. The specification does not teach the level of RB expression obtained, the level of RB expression required to obtain a therapeutic effect or that administration of the adenoviral vector and BC BigCHAP resulted in a therapeutic effect. The art at the time of filing does not teach administering adenoviral vector encoding a therapeutic protein to treat bladder cancer. Therefore, the specification does not enable delivering a therapeutic gene as claimed.

Claims 35, 36 and 40 are not enabled because they are missing essential elements. The claims are directed toward treating bladder cancer using a therapeutic gene. The therapeutic gene must be in a vector and encode a therapeutic protein operatively linked to a promoter which is considered essential to the invention. The claims do not recite the protein encoded by the gene,

administering the gene to the cell within a patient, expression of a protein encoded by the therapeutic gene to therapeutic levels or treating bladder cancer which are also essential to the invention.

Applicants arguments regarding obtaining the Impurities are noted and are discussed throughout the discussion above regarding determining the structure of the Impurities and their relationship to the claims.

Applicants argue the invention enhances gene delivery *in vivo* to obtain a therapeutic effect. Applicants argument is not persuasive. To enhance treatment of bladder cancer using a therapeutic gene using applicants invention, applicants must first enable treating bladder cancer using a therapeutic gene. Applicants do not enable treating bladder cancer using a therapeutic gene by teaching the combination of elements required to obtain such an effect using a gene delivery or by providing evidence that bladder cancer had been treated using a therapeutic gene at the time of filing.

Applicants argue they are not require to treat cancer using gene therapy. Applicants argument is not persuasive. Applicants are required to provide adequate guidance for one of skill to treat cancer using gene therapy. Example 6 does not teach the amount of RB expressed in the mice was a level adequate to treat bladder cancer. Nor are the claims limited to "intravesical administration" or the RB gene as in Example 6. Example 9 does not teach the amount of p53 is expressed to a therapeutic level. Nor are the claims limited to intrabladder administration or the p53 gene. Examples 6 and 9 do not teach the promoter used. More importantly, Examples 6 and

9 use BigCHAP which does not correlate to the claims because it has a different structure than Formula I or II. While the lot of BigCHAP used by applicants had a combination of BigCHAP, Impurities I, II and III, the claims are not drawn to using a composition comprising BigCHAP, Impurities I, II and III. Given the state of the art and the lack of guidance regarding the specific combination of elements (promoter, route of administration, expression level of RB or p53) required to target the bladder and treat bladder cancer using gene therapy, applicants do not provide adequate guidance to enable one of skill to treat bladder cancer using gene therapy as claimed.

3. Claims 21, 22, 35, 36 and 40-55 remain rejected as being indefinite because the structures encompassed by the claims are unclear for reasons of record.

The claims require a compound having Formula I or II, wherein cholic or deoxycholic acid is attached at X1. The specification (Ex. 11) states three impurities (I, II and III) were isolated from BC BigCHAP, but does not teach the structure of the impurities or how cholic or deoxycholic acid is attached to Formula I or II. The structure of the impurities (see attached) have three carbons between the carboxyl group and the pentose ring instead of four in the cholic or deoxycholic acid (i.e. the impurities require at least X1 is cholic or deoxycholic acid with a deletion of the terminal CO_2H). Addition of the cholic or deoxycholic acid would result in four carbons between the carboxyl group and the pentose ring of the cholic or deoxycholic acid which is not the structure of the impurities of BigCHAP. Therefore, it is unclear whether applicants intend the claim to encompass attaching three or four carbons between the carboxyl group and the

pentose ring. If applicants intend the claim to encompass three carbons between the carboxyl group and the pentose ring, cholic or deoxycholic acid with a deletion of the terminal O_2H is not cholic or deoxycholic acid as claimed. The limitation of attaching cholic or deoxycholic acid to X2 or X3 is rejected for the same reasons.

Applicants argue Impurity II has "Structure V" disclosed on pg 13 of the response. Applicants argument is not persuasive because "Structure V" is not disclosed in the specification. Nor are the claims limited to "Structure V".

Applicants argue the synthetic scheme on pg 6 of applicants response; therefore, applicants argue it is readily apparent how the cholic or deoxycholic acid are attached. Applicants argument is not persuasive because the Impurities are not being synthesized; they are being isolated. It is not readily apparent that the Impurities isolated from BigCHAP would have the terminal O_2H of cholic or deoxycholic acid deleted.

Claim 40 remains indefinite because is dependent upon claim 23 which has been canceled.

Claim Rejections - 35 USC § 102

The rejection of claims 41-55 under 35 U.S.C. 102(b) as being anticipated by Aungst (1993, Int. J. Pharm., Vol. 53, pages 227-235) is withdrawn. Applicants argue BigCHAP does not read on claim 41 because the tertiary nitrogen claimed is different than the tertiary nitrogen of BigCHAP. Applicants argument is persuasive.

Claim Rejections - 35 USC § 103

The rejection of claim 40 under 35 U.S.C. 103(a) as being unpatentable over Aungst (1993, Int. J. Pharm., Vol. 53, pages 227-235) in view of Carson (U.S. Patent, 5,804,566, Sept. 8, 1998) is withdrawn in view of applicants arguments regarding Aungst in the 102 rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 21, 22 and 44-55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/112074. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compound claimed in 09/112074 is a species of the compound claimed in the instant application. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER